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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/634,441	08/05/2003	Boris Skurkovich	53663-5007-02	8293

23973 7590 03/27/2007

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EXAMINER	
DEVI, SARVAMANGALA J N	
ART UNIT	**PAPER NUMBER**
1645	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/634,441	SKURKOVICH ET AL.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 March 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-10* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

RESPONSE TO APPLICANTS' AMENDMENT

Applicants' Amendment

1) Acknowledgment is made of Applicants' amendment filed 03/02/07 in response to the non-final Office Action mailed 11/30/06. With this, Applicants have amended the specification and the claims.

Status of Claims

2) Claims 11-20 have been canceled via the amendment filed 03/02/07.

Claims 1 and 9 have been amended via the amendment filed 03/02/07.

Claims 1-10 are pending and are under examination.

Supplemental Application Data Sheet

3) Acknowledgment is made of Applicants' Supplemental Application Data Sheet filed 03/02/07 in accordance with 37 CFR 1.76(c)(1) and (d)(1) that corrects the filing date of the prior application 10/372,644 from 06/21/2003 as indicated on the oath/declaration to 02/21/2003.

This application is a continuation-in-part of the application 10/372,644, filed 02/21/2003, now pending, which is a continuation of application 09/894,287, filed 06/28/2001, now US patent 6,534,059, which claims domestic priority to the U.S. provisional application 60/295,895, filed 06/05/2001.

Objection(s) Withdrawn

4) The objection to the specification made in paragraph 5 of the Office Action mailed 11/30/06 is withdrawn in light of Applicants' amendment to the specification.

Rejection(s) Withdrawn

5) The rejection of claim 9 made in paragraph 7 of the Office Action mailed 11/30/06 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicants' amendment to the claim.

6) The rejection of claims 1-7 and 10 made in paragraph 9 of the Office Action mailed 11/30/06 under 35 U.S.C. § 103(a) as being unpatentable over Jonker *et al.* (WO 90/10707 – Applicants' IDS) in view of Pluenneke (US 2001/0021380 A1), is withdrawn in light of Applicants' amendment to the base claim.

7) The rejection of claim 8 made in paragraph 10 of the Office Action mailed 11/30/06 under 35 U.S.C. § 103(a) as being unpatentable over Jonker *et al.* (WO 90/10707 – Applicants' IDS) as modified by Pluenneke (US 2001/0021380 A1) as applied to claim 1, and further in view of Skurkovich *et al.* (*Curr. Opin. Mol. Therap.* 15: 52-57, February 2003) (Skurkovich *et al.*, 2003) and Spinelli *et al.* (*Nature Struct. Biol.* 3: 752-757, September 1996), is withdrawn.

New Rejection(s) Necessitated by Applicants' Amendment

Rejection(s) under 35 U.S.C. § 103

8) Claims 1, 2 and 4-10 are rejected 35 U.S.C. § 103(a) as being unpatentable over Qian *et al.* (*Arch. Ophthalmol.* 118: 1666-1671, December 2006 – Applicants' IDS) in view of Pluenneke (US 2001/0021380 A1, already of record).

Qian *et al.* taught a method of treating a corneal transplant rejection in mice (i.e., mammal) comprising topical administration of drops or microliters of a preparation consisting essentially of a TNF alpha inhibitor such a TNFR contained in phosphate buffered saline solution (i.e., a pharmaceutically acceptable carrier). See page 1666; Materials and Methods, particularly on page 1667. In addition to documenting the the art-recognized fact that TNF-alpha could serve as an appropriate target for therapeutic intervention in prevention of corneal allograft rejection (see sentence bridging pages 1668 and 1669), Qian *et al.* presented data indicating that local neutralization of TNF-alpha activity holds promise as an effective modality for suppressing TNF-alpha-mediated processes in corneal transplantation (see top of left column on page 1671). Qian *et al.* stated that their study represents the first study providing evidence for local anti-TNF strategies, using the novel method of topically administering a soluble TNFR, for effective prevention of corneal allograft rejection. See first sentence in the third full paragraph of the right column on page 1670. Qian *et al.* further taught that there is profound and sustained up-regulation in expression of the proinflammatory cytokine, TNF-alpha protein, in allogenic corneal transplantation. Qian *et al.* also taught how therapy with anti-TNF alpha antibody has been shown to be effective in prevention and reversal of rejection episodes of other organ transplants such as cardiac allotransplantation. See page 1666; and paragraph bridging pages 1666 and 1667.

The teachings of Qian *et al.* meet the instant claims except that Qian *et al.* use a TNFR TNF-alpha inhibitor rather than an antibody to TNF-alpha in their method of treatment of corneal transplant rejection in a mammal.

However, Pluenneke expressly disclosed that a therapy that includes a TNF alpha inhibitor such as a TNFR or a TNF alpha antibody is used to treat or prevent corneal transplant rejection in human or non-human patients (see sections 0071 and 0081) and that the therapeutic administration includes administration via eyedrops (see section 0026). The antibody used is a humanized monoclonal antibody which binds specifically to human TNF-alpha or the antigen binding (i.e., biologically active) fragment thereof, or antibodies described in US 5,656,272, i.e., monoclonal, polyclonal, chimeric, heavy chain antibodies, or variable heavy chain antibodies and rodent as well as human antibodies to TNF-alpha to TNF-alpha (see section 0032).

Given Pluenneke's teaching that a TNF alpha antibody **or** a TNFR is used to treat or prevent corneal transplant rejection, i.e., the use of TNF alpha antibody as an alternative to TNF alpha inhibitor, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to replace the TNF alpha inhibitor, TNFR, in Qian's method of treating corneal transplantation with Pluenneke's polyclonal, monoclonal or humanized TNF alpha antibody or the antigen binding fragment thereof, or heavy chain antibodies or variable heavy chain antibodies to TNF-alpha, to produce the method of the instant invention. Because both TNFR and TNF alpha antibody were art-recognized TNF alpha inhibitor equivalents in treating corneal transplant rejection at the time of the invention as shown by Pluenneke, both having TNF alpha-inhibiting functions, one of ordinary skill in the art would have found it obvious to substitute a TNFR with a TNF alpha antibody. The substitution of one TNF alpha inhibitor with another, alternative, art-known TNF inhibitor such as an antibody to TNF-alpha, which has the same TNF inhibiting function, was well within the realm of routine experimentation, would have been obvious to a skilled artisan at the time of the invention, and would have yielded similar therapeutic effects.

Claims 1, 2 and 4-10 are *prima facie* obvious over the prior art of record.

9) Claim 3 is rejected 35 U.S.C. § 103(a) as being unpatentable over Qian *et al.* (*Arch. Ophthalmol.* 118: 1666-1671, December 2006 – Applicants' IDS) as modified by Pluenneke (US 2001/0021380 A1, already of record) as applied to claim 1 above.

The teachings of Qian *et al.* as modified by Pluenneke are explained above which do not specifically disclose that the mammal treated in their method is a human.

However, given Pluenneke's disclosure of the administration of an anti-TNF alpha antibody to human patients (see section 0081), it would have been *prima facie* obvious to one of

ordinary skill in the art at the time the invention was made to extend Qian method as modified by Pluenneke to humans having rejection of a corneal transplant to produce the method of the instant invention. Extending the prior art method of treatment from a non-human mammal to a human mammal having rejection of a corneal transplant was well within the realm of routine experimentation, would have been obvious to one of ordinary skill in the art, and would have yielded similar results given that studies in animals or animal models are routinely and conventionally extended or extrapolated in the art to human situations.

Claim 3 is *prima facie* obvious over the prior art of record.

Relevant Prior Art

10) The prior art made of record and not relied upon in any of the rejections is considered pertinent to Applicants' disclosure:

- Skurkovich *et al.* (*Int. J. Immunotherapy* XIV (1): 23-32, 1998) taught monotherapy for autoimmune diseases with antibodies to TNF-alpha. Skurkovich *et al.* identified autoimmune diseases of the eye and transplant rejection as autoimmune conditions or diseases with cytokine disturbance which could be treated by anticytokine therapy. Skurkovich *et al.* administered only TNF-alpha antibodies to patients with certain types of autoimmune diseases and showed that antibodies to TNF-alpha alone exerted an immediately apparent beneficial influence. See summary; and pages 24, 29 and 30.

- Le *et al.* (US 5,656,272) taught monoclonal, polyclonal, chimeric, heavy chain, or variable heavy chain antibodies and rodent as well as human antibodies to TNF-alpha. See entire document including abstract; the 'TNF Antibodies' section; 'Anti-TNF Antibodies and Methods'; and 'Summary of the Invention'.

- Skurkovich *et al.* (US 6,333,032) taught the availability in the art of TNF alpha antibody and its topical administration in a method of treating a patient, including a human patient, with an autoimmune conditions, including autoimmune diseases of the eye and rejection of transplantation of tissues and organs. See first paragraph in column 7; and paragraph bridging columns 17 and 18; lines 44-49 in column 12; and paragraph bridging columns 12 and 13; the sentence bridging columns 18 and 19; Table 1; and lines 21-25 in column 11. The antibody is polyclonal, monoclonal, humanized, chimeric, single chain antibody, or biologically active fragments, or allelic variants or species thereof (see paragraph bridging columns 14 and 15; and column 15). The antibody can be from any animal species (see sixth full paragraph in column 15).

Remarks

11) Claims 1-10 stand rejected.

12) Applicants' amendment necessitated the new ground(s) of rejection presented in this Office action. **THIS ACTION IS MADE FINAL.** Applicants are reminded of the extension of time policy as set forth in 37 C.F.R 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. The Fax number for submission of amendments, responses and/or papers is (571) 273-8300, which receives transmissions 24 hours a day and 7 days a week.

14) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

15) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Jeffrey Siew, can be reached on (571) 272-0787.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

March, 2007

S. DEVI, PH.D.
PRIMARY EXAMINER